# Anemia of Chronic Kidney Disease

Ajay K. Singh

*Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

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Anemia is a common complication in patients with chronic kidney disease (CKD). Recombinant erythropoietin (epoetin) has been the most important advance in treating this anemia. Erythropoietin was approved by the Food and Drug Administration (FDA) in 1989. Although the initial goal of treating CKD anemia with epoetin was to prevent blood transfusions, evidence from prospective studies also demonstrated marked attenuation in the symptoms of anemia (1–3). Subsequently, several observational studies have demonstrated associations between anemia and harder outcomes, such as mortality and cardiovascular complications (4–6). Likewise, studies have documented an association between the severity of anemia and left ventricular hypertrophy (LVH) (7,8). By the early to mid-1990s, the majority of dialysis and non-dialysis CKD patients and many patients without CKD were receiving epoetin therapy. The benefits of epoetin therapy resonated among patients and providers alike: Preventing blood transfusions, improving quality of life, improving survival, and reducing cardiovascular complications including heart failure and LVH. Between 1991 and 2005, the target and achieved levels of hemoglobin (Hb) increased, with mean Hb in hemodialysis patients being raised from 9.7 to 12 g/dl (9). The publication of the Normal Hematocrit study in 1998 (10) and more recently the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) (11) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin $\beta$ (CREATE) (12) studies have precipitated FDA advisories (13) about achieving a Hb in the 10- to 12-g/dl range. A narrow Hb target range and the observation that Hb varies in the majority of patients with CKD make treating anemia quite challenging. The reports of pure red cell aplasia (PRCA) from neutralizing antierythropoietin antibodies has also generated considerable concern about the safety of epoetin. Finally, despite ongoing worries about epoetin therapy, newer erythropoiesis-stimulating agents (ESA) have emerged. This issue of *CJASN* contains three articles on various aspects of epoetin therapy and anemia management in patients with CKD. Two of these are mini-reviews, and one is an original article.

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**Correspondence:** Dr. Ajay K. Singh, Renal Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Phone: 617-732-5951; Fax: 617-732-6392; E-mail asingh@partners.org

## Newer ESA

The market opportunity for the pharmaceutical industry from epoetin has not gone unnoticed to the pharmaceutical world. An estimated $22 billion worth of Epogen has been sold (14). A derivative of epoetin-$\alpha$, darbepoetin, has also been a success. More recently, Continuous Erythropoiesis Receptor Activator (CERA), a derivative of epoetin-$\beta$, has been approved by the FDA. Epoetin is now Medicare's largest single pharmaceutical expense, costing approximately $2 billion in 2005 (15). Several companies have or are developing ESA. In this issue of *CJASN*, Macdougall (16) reviews the recent progress in developing epoetin analogues or derivatives.

## ESA-Induced PRCA

A thorny problem in treating patients with CKD anemia is the syndrome of PRCA. In the late 1980s, the first reports of PRCA associated with epoetin therapy were published (17). PRCA is a marrow failure syndrome complex characterized by selective reduction or absence of erythroid precursors with maturation arrest at the basophilic pronormoblastic phase in the bone marrow associated with reticulocytopenia and anemia (18). The mini-review by Pollock *et al.* (19) in this issue of *CJASN* provides a comprehensive review of epoetin-induced PRCA. All of the epoetin molecules that are on the market (epoetin-$\alpha$, darbepoetin, and epoetin-$\beta$), regardless of the manufacturer, have been reported in inducing cases of PRCA. In 2002, in a seminal article, Casadevall *et al.* (20) reported 13 cases of PRCA in patients who received epoetin subcutaneously. Between 1998 and 2000, nearly 200 cases of epoetin-associated PRCA cases were reported (21). Most cases occurred outside the United States and were attributed to the substitution of Tween in place of human serum albumin as a stabilizer for epoetin (22–24). The interaction of Tween with the uncoated rubber in prefilled syringes seems to cause leachates. These leachates have been implicated in causing aggregation of epoetin molecules, enhancing their antigenicity. Although some unanswered questions remain, such as why only a fraction of patients who are exposed to epoetin that is contaminated by leachates develop PRCA, modifications in the manufacturing and storage of epoetin have resulted in a dramatic (>80%) reduction in the reported cases of PRCA (21). Pollock *et al.* (19) provide a detailed description of the syndrome and its management and correctly advise clinicians to be vigilant of this syndrome.



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## Hb Variability and Target Hb in Patients with CKD

Complicating the management of anemia in dialysis patients is the problem of Hb variability. This is because virtually all dialysis patients demonstrate some degree of Hb variability. Hb variability takes on significance because of the importance of keeping Hb concentrations >10 and <12 g/dl as recommended most recently by the FDA (13). In the revised 2006 National Kidney Foundation Dialysis Outcomes Quality Initiative anemia guidelines (25), a minimum Hb target of 11g/dl was recommended without specification of a maximum target level. The National Kidney Foundation Work Group "rejected, identifying a target Hb level bounded by narrow upper and lower values (*e.g.*, 11.0 to 12.0 g/dl). Such a target affords neither clarity nor simplicity, is possible to achieve in only a minority of patients, discourages flexibility in managing individual patients, and likely promotes cycling of Hb results greater than and less than the target" (25). In 2007, another update of the anemia guidelines narrowed the recommended target Hb range to 11 to 12 g/dl but continued to emphasize the issue of Hb variability (26).

Why is the Hb target range of such great importance? Part of the answer comes from the results of the Normal Hematocrit Study (NHS) (10). NHS was a randomized, controlled study of hemodialysis patients with established heart disease. It sought to test whether complete correction of anemia with high dosages of epoetin in dialysis patients was superior to partial correction of anemia with lower dosages of epoetin. The study randomly assigned patients to a hematocrit target of 42 *versus* 30%. The study was stopped by the Data Safety Monitoring Board because of increased risk in the higher Hb arm. In the published study of 1233 patients, the higher hematocrit group showed a strong trend for a higher rate of nonfatal myocardial infarction or death (relative risk 1.3; 95% confidence interval [CI] 0.9 to 1.9); the FDA recently reported the final study results, showing evidence for harm in the patients who were randomly assigned to the higher Hb arm (27) (relative risk 1.28; 95% CI 1.06 to 1.56; $P < 0.01$ log rank test). In 2006, the CHOIR study reported similar results but in nondialysis patients with CKD. CHOIR was an open-label, randomized trial that studied 1432 patients with CKD to receive epoetin targeted to achieve a Hb of 13.5 *versus* 11.3 g/dl (11). Increased risk was reported for patients who were randomly assigned to the higher Hb arm (hazard ratio 1.34; $P = 0.03$l). CREATE, using a similar design as CHOIR, reported a trend for increased risk for targeting a higher Hb level, albeit the study was underpowered (12). The Canada-Europe study using softer end points failed to report a benefit of targeting a higher Hb concentration (28). Indeed, several randomized, controlled studies have failed to demonstrate a benefit of targeting a higher Hb in arresting or even slowing progression of LVH (12,28–31); therefore, current evidence suggests that targeting higher Hb (to levels >12 g/dl) with higher dosages of epoetin is either of no benefit or associated with increased risk. Conversely, observational data suggest that too low of a Hb concentration is associated with higher risk (a higher rate of mortality and cardiovascular complications) (4–6), as well as a higher rate of blood transfusions and possibly worse quality of life. Thus, a consensus has emerged that, notwithstanding variability, the Hb concentration should be 10 to 12 g/dl in patients with CKD, a recommendation recently underlined by the FDA in a public advisory (27); however, are transient excursions outside this range clinically important? Are these transient excursions more important at the higher end of the Hb range (*i.e.*, at the 12-g/dl ceiling) or at the lower end of the Hb range (*i.e.*, the 10-g/dl Hb floor)? Although several studies demonstrated that Hb variability is a common occurrence in dialysis patients (32–35), the clinical significance of transient excursions is less clear. Some have suggested that these excursions may be associated with worse outcome, such as episodic myocardial ischemia because of the effect of Hb levels oscillating in and out of the desired range.

The study by Gilbertson *et al.* (36) in this issue of *CJASN* explores the relationship between Hb variability and mortality. The authors used a Fresenius cohort that comprised 159,720 long-term hemodialysis patients. They assessed the degree of Hb variability in the first 6 mo of 2004 and then evaluated the effect on mortality in the subsequent 6 mo. Monthly Hb values were categorized as follows: Low (Hb <11.0 g/dl), intermediate (Hb 11 to 12.5 g/dl), and high (Hb >12.5 g/dl). Variability in Hb was categorized by developing different combinations of the Hb categories: Low-low, high-high, low-high, and so forth. Gilbertson *et al.* report that transient excursions from the 11- to 12-g/dl Hb range are quite common. Furthermore, they report that patients with Hb variability at the low end of the Hb range as well as patients with Hb falling to a low Hb concentration had the highest risk for mortality. In contrast, patients with variability at the high Hb level or patients with high Hb concentrations did not demonstrate any excess mortality. The study had several strengths: First, this was a very large cohort; second, unlike previous studies, this was a contemporary cohort. Finally, the authors used a Bayesian approach in their analyses; however, the study had two overwhelming limitations: The authors did not adjust for important laboratory confounders (*e.g.*, markers of inflammation). Second, the authors failed to use time-varying models that have become established in evaluating data such as these (*i.e.*, characterized by time trends and a high degree of confounding). The analysis was also limited by its examination of only short-term outcomes: Mortality during a 6-mo period. In a recent analysis, Feldman and colleagues reported a similar association between Hb variability and outcome (35). These authors also performed a retrospective analysis; however, although the sample was smaller (19,150 of 34,963 dialysis patients from the Fresenius Medical Care database) and less contemporary than the study by Gilbertson *et al.*, Feldman and colleagues used a more robust definition of Hb variability: The residual SD of Hb. As well, Feldman and co-workers adjusted for several key laboratory covariates, including serum albumin, aspartate aminotransferase, calcium, intact parathyroid hormone level, and iron level. They also used time-varying analytic approaches to construct their models. Feldman's survival analyses demonstrated that each 1-g/dl increase in the Hb residual SD was associated with

a mortality hazard ratio of 1.33 (95% CI 1.22 to 1.45) even after adjusting for multiple covariates.

## Conclusion

Erythropoietin is arguably the best example of the therapeutic benefits of molecular biology/biotechnology in clinical medicine. In treating CKD anemia, recombinant erythropoietin has benefited millions of patients. It has spawned the development of newer derivatives that may be cheaper and more convenient to use; however, with success has come problems, and these have generated considerable controversy. The articles in this issue of *CJASN* examine some of these issues.

## Disclosure

A.K.S. has received consulting fees from Ortho Biotech Clinical Affairs/Johnson & Johnson, Amgen, Roche, Abbott, and Watson and lecture fees from Ortho Biotech Clinical Affairs/Johnson & Johnson, Roche, Amgen, Abbott, Watson, and Genzyme; has served on advisory boards for Ortho Biotech Clinical Affairs, Roche, Watson, AMAG, and Amgen; and has received grant support from Ortho Biotech Clinical Affairs, Dialysis Clinics, Roche, Baxter, Johnson & Johnson, Amgen, Watson, and Aspreva. A.K.S. is also a medical director of Dialysis Clinics Inc.

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See related articles, "Novel Erythropoietic Agents: A New Era in Anemia Management," on pages 200–207, "Pure Red Cell Aplasia Induced by Erythropoiesis-Stimulating Agents," on pages 193–199, and "Hemoglobin Level Variability: Associations with Mortality," on pages 133–138.